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# Neurobehavioural Evaluation of Antidepressant and Anticonvulsant Potentials of Tizanidine in Balb/c Mice

**Esther B. Patrick[1,2], Sunday O. Otimenyin[1], Bukata B. Bukar[1], Ben A. Chindo[2], Danjuma Mallam[2]**

[1]Department of Pharmacology, Faculty of Pharmaceutical Sciences, University of Jos, Jos, Nigeria
[2]Department of Pharmacology and Toxicology, Kaduna State University, Kaduna, Nigeria

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## ABSTRACT

Tizanidine is a selective α2-adrenergic receptor agonist that stimulates the central nervous system through the adrenergic pathway. This study evaluated the antidepressant and anticonvulsant activity of tizanidine in mice. The various limitations of currently available anti-depressive and epileptic drugs and the bidirectional relationship between the two neurological disorders warrant improved pharmacotherapy interventions. 125 Balb/c mice were divided into 75 and 50 for antidepressant and anticonvulsant studies, respectively. Forced swim (FST), tail suspension (TST), and open field (OFT) antidepressant models were used. In each model, twenty-five mice were divided into five groups (n=5); 1 mL/kg distilled water group (negative control), 15 mg/kg imipramine (positive control in FST and TST), 0.05 mg/kg diazepam (positive control for OFT) group, and 1 mg/kg, 2 mg/kg, and 4 mg/kg tizanidine groups respectively. Anticonvulsant screening was conducted using pentylenetetrazole (PTZ) and picrotoxin models of seizure in which mice were treated with 2 mg/kg, 4 mg/kg and 8 mg/kg tizanidine. Tizanidine at all the doses significantly reduced the immobility time of the mice in FST ($p \leq 0.0001$) and TST ($p \leq 0.05$). There was no significant increase in line crossing frequency between tizanidine and 0.05 mg/kg diazepam in the OFT ($p > 0.05$). Tizanidine significantly delayed the onset of myoclonic jerks ($p \leq 0.001$) in the PTZ model but not in the picrotoxin model ($p > 0.05$). This study showed that tizanidine possesses antidepressant-like activity, but little anticonvulsant activity.

**Keywords:** *Depression; Antidepressant; Epilepsy; Anticonvulsant; Tizanidine; α2-adrenoreceptor*

## INTRODUCTION

Epilepsy and depression are chronic neurological disorders affecting more than 50 to 264 million people worldwide (Kroner et al. 2016; James et al. 2018). People with these disorders are associated with significant physical, mental, psychological and socioeconomic problems. In adiition, pharmacological and non-pharmacological treatment modalities for these illnesses burden the healthcare systems. To top it all, up to 25% of epileptic patients are therapy-resistant (Brodie et al. 2012), whilst about 80% of depressed patients relapse after treatment (Mueller et al. 1999).

Life expectancy is reduced, and the prevalence of suicidal ideation/suicide is very high; in epilepsy, up to 10% have suicidal ideation (Bosak et al. 2016) and more than 60% in depressed patients (Nock et al. 2009). Current findings show that these two disorders have a bidirectional relationship, with each neurological disorder acting as a risk factor for each other. Wiegartz et al. (1999) reported that 43% of patients with epilepsy had a major depressive disorder, while patients with depression have a three to seven-fold higher risk of developing epilepsy

Correspondence: Esther B. Patrick, MSc; Department of Pharmacology, Faculty of Pharmaceutical Sciences, University of Jos, Jos, Nigeria; Email: ebadugupatrick@gmail.com; Phone: +234 8184890534; ORCID: 0000-0003-1393-5035

(Forsgren and Nystrom 1999; Hesdorffer et al. 2000, 2006). These data may be explained by the existence of common pathogenic mechanisms operant in both conditions (Kanner 2009), with the presence of one disorder potentially facilitating the development of the other. Kanner (2005) showed that both epilepsy and depression share the following pathogenic mechanisms; structural changes presenting as atrophy of temporal and frontal lobe structures, in the amygdala, hippocampus, entorhinal cortex, and temporal and lateral neocortices among others; functional abnormalities in the temporal and frontal lobes consisting of decreased 5-HT1A binding in the mesial structures, raphe nuclei, thalamus, and the cingulate gyrus; hyper-functional hypothalamic–pituitary–adrenal axis and abnormal central nervous system (CNS) activity of several neurotransmitters, particularly serotonin, noradrenaline, dopamine, GABA, and glutamate.

This study is based on the hypothesis associating depression and epilepsy to hyper-functional excitatory neurotransmitter glutamate. It presumes excessive glutaminergic activity as the major pathological link in both epilepsy and depression. Given this assumption, we speculate that an agent that acts on a receptor with a predominately inhibitory effect at excitatory neuron will be a potent antidepressant and antiepileptic agent. Thus, tizanidine (5-chloro-4-(2-imidazolin-2-yl-amino)-2,1,3-benzothiadazole hydrochloride), an α2-adrenoreceptor agonist was used.

The bases of this assumption is the finding that excessive glutamatergic activity at N-methyl- D-aspartate (NMDA) receptors is associated with depression and antagonizing the NMDA receptor with ketamine producing a fast antidepressant effect (Berman et al. 2000; Zarate et al. 2006). More so, excessive neuronal glutaminergic hyperactivity results in the evolution of abnormal neuronal excitability in epilepsy (Engel 2013). In all, these suggest that depression and epilepsy are associated with hyper-functional glutaminergic activity.

Zhang et al. (2009) showed that α2-adrenergic receptor activation contributes to the antidepressants effect of noradrenalin reuptake inhibitor, desipramine, suggesting the possibility of tizanidine being a good antidepressant. Other studies also suggest that the stimulation of the presynaptic α2-adrenergic receptor by tizanidine inhibits the release of excitatory amino acid, which stimulates the NMDA receptor (Maeda-Hagiwara et al. 1986; Maze and Tranquilli 1991; Koyuncuŏglu et al. 1992). The above studies support the possible antiepileptic and antidepressant potential of tizanidine. Thus, this work evaluated the antidepressant and antiepileptic potentials of the α2-adrenergic receptor agonist tizanidine in mice using neurobehavioural studies.

## MATERIALS AND METHODS

### Animals Used

Adult Swiss Balb/c mice of both sexes (20 - 30g) bred in the animal house facility of the Department of Pharmacology and Toxicology of the Kaduna State University and the University of Jos, Nigeria, were used for the antidepressant and anticonvulsant studies, respectively. The animals were maintained freely on standard pellets and water all through breeding and during the study.

Permission and approval for the animal studies was from the Animal Ethics Committee, Department of Pharmacology, Faculty of Pharmaceutical Sciences, University of Jos, with approval number; F17-00379. In addition, all animal experiments complied with the National Institute of Health Guide for Care and Use of Laboratory Animals.

### Experimental Design

One hundred and twenty-five mice were divided into 75 and 50 for antidepressant and anticonvulsant studies, respectively. In order to evaluate the antidepressant effect of tizanidine, the 75 mice were subdivided into three groups of 25 mice each. The first 25 mice were subjected to a forced swim test (FST), the second 25 underwent a tail suspension test (TST), and the last 25 mice were assessed in open field, the open field test (OFT).

The 50 mice for the anticonvulsant study were subdivided into two groups of 25 each. The anticonvulsant potential of tizanidine was assessed in the first 25 mice using pentylenetetrazole (PTZ) model, while the picrotoxin model of seizure was assessed with remaining 25.

### Antidepressant Screening Test

The method of Patrick et al. (2018) was adopted for the antidepressant study. Forced Swim, tail suspension and open field tests models were used. Each model had twenty-five mice that were further subdivided in to five groups of five animals each.

### Forced Swim Test (FST)

In the FST; a modified version of Porsolt et al. (1977) was adopted. Mice were grouped and treated with, 1 mL/kg distilled water (negative control), 15 mg/kg imipramine (Mallinckrodt Pharmaceuticals, Canada, positive control), and 1 mg/kg, 2 mg/kg and 4 mg/kg of tizanidine. All administrations were carried out intraperitoneally before the test. Mice were individually placed in a plastic cylindrical tank (46 cm height × 20 cm diameter) filled with tap water (25 ± 1ºC) to a depth of 20 cm, thirty minutes post-treatment, and observed for 6 min. During this period, the immobility time (a measure of depressive state of decrease resilience and increase hopelessness) of the animals was recorded within the last 4 min. Mice were considered immobile when they remain floating without struggling and making only slight movements neces-

sary to maintain the head above the water. Fresh water was used for each mouse and mice were dried at the end of each test period.

**Tail Suspension Test (TST)**

The TST was conducted using standard procedure (Steru et al. 1985). Mice were similarly grouped and treated as in the FST model. Thirty minutes post-treatments, mice were individually suspended vertically at 15 cm on a tail suspension test apparatus with an adhesive tape placed 1 cm away from the tip of the tail. Immobility period, a measure of depressive state of decrease resilience and increase hopelessness was recorded within 6 min of the test. Mice were considered to be immobile when they did not show any movement of the body and hanged passively. Before the introduction of each mouse, the space used was cleaned with 70% ethanol to prevent behavioural change from olfactory cues.

**Open Field Test (OFT)**

The OFT was performed using standard procedure by Walsh and Cummins (1976) with a little modification. Mice were similarly grouped and treated as in the other two models though the positive control group were treated with 0.05 mg/kg Diazepam. Thirty minutes post-treatment, mice were individually placed in the centre square of the open field apparatus and locomotor activity measured as the latency to leave centre square, and the total square crossed with all four paws. These were recorded within 5 min. At the end of each test, each mouse was removed and the box cleaned with 70% ethanol before testing the next mouse.

**Assessment of Antiepileptic Activity**

Tizanidine (DS 103-282, Sandoz Novartis, India) was screened for anticonvulsant effect using PTZ and picrotoxin seizure models. In the PTZ model, twenty-five mice were randomly divided into five groups (n=5); 1 mL/kg distilled water group (negative control), standard drug group (phenobarbital, 30 mg/kg, David Bull Laboratories, Australia), and 2 mg/kg, 4 mg/kg, and 8 mg/kg tizanidine test groups. The same grouping arrangement was also use for the picrotoxin model; 1 ml/kg distilled water group (negative control), standard drug group (diazepam 10 mg/kg, Roche, Switzerland), 2 mg/kg, 4 mg/kg, and 8 mg/kg tizanidine test groups.

A modified method of Chindo et al. (2009) was adopted for the anticonvulsant study. Thirty minutes post treatments, standard convulsive agents, PTZ, (85 mg/kg, Sigma Chemical Co. USA) and picrotoxin (10 mg/kg, Sigma Chemical Co. USA) were used to induce seizures in the mice. All administrations were carried out intraperitoneally. Following administration of convulsive agents, mice were placed individually in a behavioural box and observed for the onset of first myoclonic jerks, and hind limb extension. Percentage protection from death was also noted. The ability of the tizanidine to prevent or delay the onset of hind limb extension in the animals was taken as an indication of anticonvulsant activity (Amabeoku and Chikuni 1993).

**Statistical Analysis**

The data were analysed using one-way analysis of variance (ANOVA), followed by Bonferroni post hoc test for multiple comparison using statistical package for social sciences (SPSS version 25). P≤0.05 was considered statistically significant. Results were expressed as mean ± standard error of mean.

## RESULTS

**Antidepressant Action**

**Force Swim and Tail Suspension Tests**

Tizanidine at all doses and 15 mg/kg imipramine significantly decreased immobility time in mice in the FST [F (4, 20) = 33.25, p=0.000], and in the TST [F (4, 20) = 5.58, (p=0.003)] for imipramine, with p=0.04, 0.03 and 0.05 for the 1 mg/kg, 2 mg/kg, and 4 mg/kg tizanidine respectively, when compare with control mice (Fig. 1)

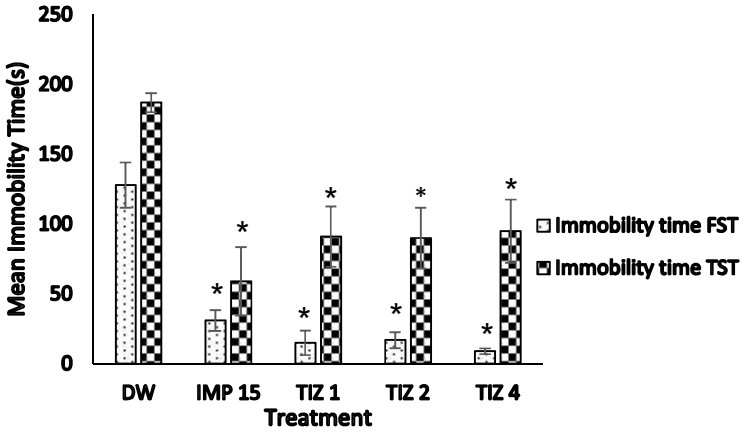



**Fig. 1: Effect of distilled water, imipramine, and tizanidine on immobility time in mice FST and TST**. Each column represents mean ±SEM. n=5. * Significant at p≤0.0001 vs distilled water group. DW=distilled water, 15 IMP= 15 mg/kg Imipramine, TIZ 1= 1 mg/kg Tizanidine, TIZ 2= 2 mg/kg Tizanidine, TIZ 4 = 4 mg/kg

**Open Field Test**

In the OFT, tizanidine at all doses and diazepam (0.05 mg/kg) significantly [F (4, 20) = 4.78] decreased total square crosses (p=0.05 for diazepam, p=0.02, 0.01 and 0.05 for 1 mg/kg, 2 mg/kg and 4 mg/kg tizanidine respectively). There was no significant difference in the latency to leave the centre square [F (4, 20) = 1.05, p= 0.41], between all the groups (Fig. 2)

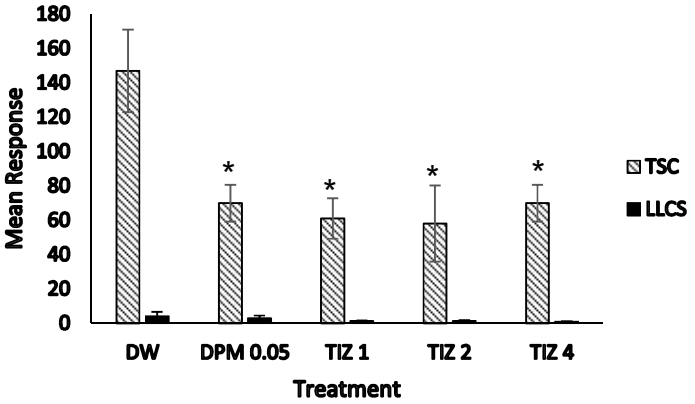



**Fig. 2: Effect of distilled water, diazepam, tizanidine on locomotor activity of mice in OFT**. Each column represents mean ±SEM. n=5. *Significant at p≤0.05 vs distilled water group. DW=distilled water, DZP 0.05= diazepam 0.05 mg/kg, TIZ 1= 1 mg/kg Tizanidine, TIZ 2= 2 mg/kg Tizanidine, TIZ 4 = 4 mg/kg. TSC = total square crossing, LLCS= latency to leave centre square.

### Antiepileptic Action

#### Pentylenetetrazole-Induced Seizures

Tizanidine at all doses significantly [F (4, 20) = 13.7], prolonged the onset of the first myoclonic jerks when compared with control mice (p=0.000 for 2 mg/kg, and 8 mg/kg, p= 0.007 for 4 mg/kg). More so, 2 mg/kg and 8 mg/kg tizanidine also significantly prolonged the onset of the first myoclonic jerks when compared with 30 mg/kg phenobarbital treated mice (p=0.02 for 2 mg/kg and p=0.01 for 8 mg/kg) (Fig. 3). Tizanidine (4 mg/kg) significantly prolonged (p=0.006) the onset of hind limb extension when compare with the control group. Whereas there was no significant (p>0.05) difference in the onset of hind limb extension between mice treated with 2 mg/kg and 8 mg/kg tizanidine and control mice (Fig. 4).

All the mice in the distilled water and 2 mg/kg tizanidine groups died, while three mice died in each of the 4 mg/kg and 8 mg/kg tizanidine groups. Two out of the five mice in 4 mg/kg and 8 mg/kg tizanidine groups survived, while all the mice treated with phenobarbital survived (Table 1).

#### Picrotoxin-Induced Seizure

Tizanidine at all doses had no effect (p>0.05) on the onset of myoclonic jerks, and hind limb extension (Fig. 3 and 4). All the mice treated with tizanidine and distilled water died while all the mice treated with diazepam survived (Table 1).

## DISCUSSION

Tizanidine caused a significant antidepressant-like effect at the dose tested as indicated by reduction in immobility time of mice in the FST (p<0.0001) and the TST (p<0.05). The efficacy of tizanidine was found to be similar to imipramine. There was no significant increase in the number of line crosses between the diazepam and the tizanidine groups in the OFT. This implies that tizanidine may not act as a stimulant, but through another antidepressant pathway, the inhibition of the NMDA receptor (Maeda-Hagiwara et al. 1986; Maze and Tranquilli 1991).

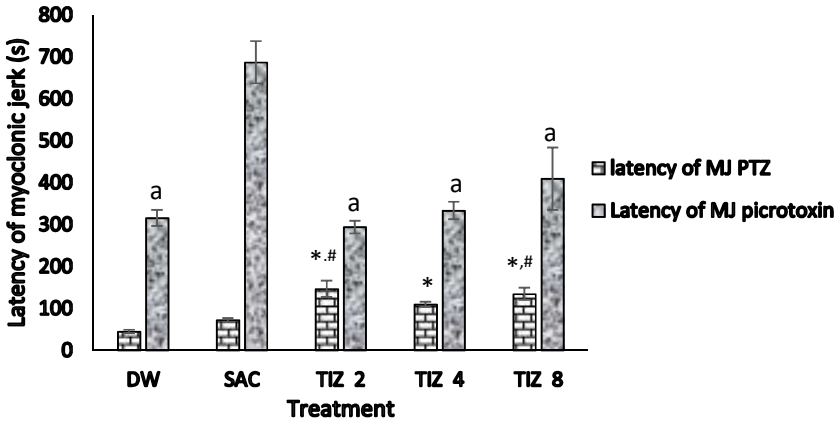
Tizanidine stimulates aspartergic and glutaminergic systems by inhibiting aspartic and glutamic acids release (Berkman et al. 1998), which may have been the case in the present study. Targeting other molecular sites aside those already streamlined for the treatment of depression is necessary. Molecules like monoamine transporters, being the major molecular target for antidepressants have been implicated in the actions of desipramine. Dziedzicka-Wasylewska et al. (2006) showed that noradrenalin transporter knock-out mouse still retained their antidepressant response to desipramine, indicating that it also acts through other pathways. The antidepressant effect of desipramine was found to be via activation of α2-adrenergic receptor (Zhang et al. 2009) and α2-adrenergic receptor down-regulation (Subhash et al. 2003).

Cottingham et al. (2012) reported that desipramine directly down-regulates endogenously expressed α2 heteroreceptors in the absence of norepinephrine or

**Table 1: Protection against Pentylenetetrazole and Picrotoxin-induced Seizures in Mice**

| Treatment/Dose | Pentylenetetrazole | | Picrotoxin | |
|---|---|---|---|---|
| | Protection from death | %Protection | Protection from death | %Protection |
| DW 1 (mL/kg) | 0/5 | 0 | 0/5 | 0 |
| Phenobarbital (30 mg/kg) | 5/5 | 100 | - | - |
| Diazepam (10 mg/kg) | - | - | 5/5 | 100 |
| Tizanidine (2 mg/kg) | 0/5 | 0 | 0/5 | 0 |
| Tizanidine (4 mg/kg) | 2/5 | 40 | 0/5 | 0 |
| Tizanidine (8 mg/kg) | 2/5 | 40 | 0/5 | 0 |

Data are presented as number of animals protected against mortality out of five animals per group. DW=distilled water




**\Fig. 3: Effect of distilled water, phenobarbital, diazepam, tizanidine on the latency of PTZ and picrotoxin-induced myoclonic jerk.** Each column represents mean ± SEM. n=5. * Significant vs distilled water in PTZ model, p≤0.05. # Significant verses 30 mg/kg phenobarbital in PTZ model, p≤0.05. [a] significant verses diazepam in picrotoxin model, p≤0.05. DW=distilled water, SAC=standard anticonvulsant; phenobarbital 30 mg/kg for PTZ model and diazepam 10 mg/kg for picrotoxin model. TIZ 2= 2 mg/kg tizanidine, TIZ 4= 4 mg/kg tizanidine, TIZ 8 = 8 mg/kg tizanidine, MJ= myoclonic jerk

norepinephrine transporter. This suggests that direct excessive activation of α2-adrenoceptor by an agonist like tizanidine may also down regulates this heteroreceptor. Another possible mechanism of antidepressant by tizanidine may be via activation and down-regulation of endogenously expressed α2 heteroreceptors. Previous studies showed that repeated or chronic stimulation of a receptor by a ligand can result in its down-regulation (Tan et al. 2004). More so, several studies found α2-adrenoceptor up-regulation (Meana et al. 1992; Callado et al. 1998; García-Sevilla et al. 1999; Ordway et al. 2003; Escriba et al. 2004) and super sensitivity (González-Maeso et al. 2002) in patients with depression, thus, inferring this process as a possible pathological mechanism of depression.

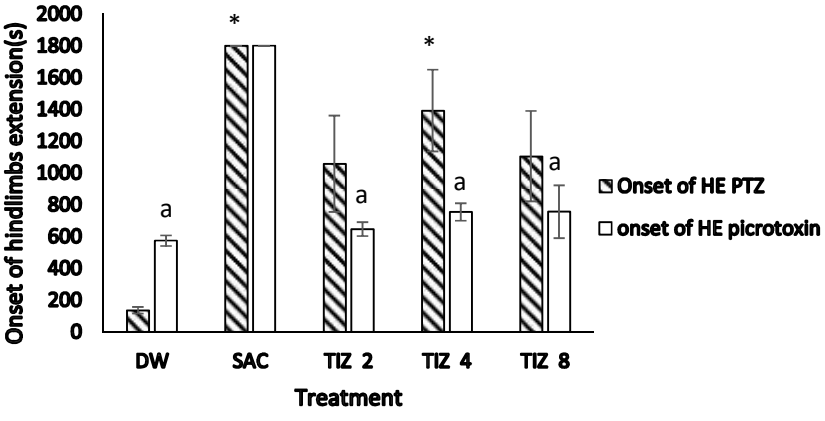



**Fig. 4: Effect of distilled water, phenobarbital, diazepam, tizanidine on the onset of PTZ and picrotoxin-induced hindlimbs extension.** Each column represents mean ± SEM. n=5. * Significant verses distilled water in PTZ model, p≤0.05. [a] significant verses diazepam in picrotoxin model, p≤0.05. DW=distilled water, SAC=standard anticonvulsant; phenobarbital 30 mg/kg for PTZ model and diazepam 10 mg/kg for picrotoxin model. TIZ 2= 2 mg/kg tizanidine, TIZ 4= 4 mg/kg tizanidine, TIZ 8 = 8 mg/kg tizanidine. HE=hindlimbs extension

Tizanidine produced some anticonvulsant-like effect in the PTZ model of seizure since the onset of the myoclonic jerks were significantly ($p<0.001$) prolonged in the doses used in the present study. The 2 mg/kg and 8 mg/kg tizanidine significantly delayed the onset of the myoclonus jerks more than the standard anticonvulsant, phenobarbital. However, the 4 mg/kg tizanidine delayed the onset of hindlimb extension when compared with the control mice, which was very minimal. 4 mg/kg and 8 mg/kg tizanidine slightly increased survival rate by 40% but not 2 mg/kg tizanidine. The implication is that, tizanidine offered some form of neuronal protection. The neuroprotective effect of α2-adrenoceptor agonist and that of tizanidine itself have been reported in other studies (Maier et al. 1993; Berkman et al. 1998; Zhang 2004).

Tizanidine showed no anticonvulsant effect in the picrotoxin model. The poor anticonvulsant activity of tizanidine may be due to the chemical, picrotoxin whose properties are different, although with similar GABA inhibitory action just like PTZ. The report by Boehm (1999) that presynaptic α2-adrenoceptor control mainly excitatory transmission, may explain the lack of anticonvulsant effect of this α2-adrenoceptor agonist, in the picrotoxin model of seizure. This also suggests that the modest anticonvulsant effect observed in PTZ model may be due to the ability of tizanidine to block neuronal excitation mediated by the NMDA receptor (not tested in this study). This may be so because reports by Velisek et al. (1999) and Yudkoff et al. (2006) showed that activation of the NMDA receptor is also involved in the initiation and propagation of PTZ- induced seizure. Although the major mechanism in which PTZ causes seizure is via GABA.

## Conclusion

This study suggests that tizanidine

has antidepressant like effect in mice FST and TST models of depression and possesses little anticonvulsant activity in seizure induce by PTZ but no activity in picrotoxin model of seizure. Further studies to validate the role of α2-adrenergic receptor activation in tizanidine's antidepressant like effect will be conducted.

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Nil.

**Conflict of Interest**
None declared.

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**Authors Contribution**
EBP, SOO, BBB and BAC – Conceptualization, research design; EBP and DM – Carried out experiment; SOO and BBB - Verified data collected; SOO, BBB, BAC and DM - Wrote draft manuscript; EBP and DM - analysed data.

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